A Survey of Cleaning Validation General Principles and Best Practices

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Overview

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I. Introduction

Objectives

A survey - “What are the primary considerations for CV?”

Discuss Cleaning Validation in the context of regulatory guidelines:

- FDA Guidances (Process Validation Life Cycle)
- International Committee on Harmonization
- WHO
- Pharmaceutical Inspection Cooperation Scheme (PIC/S)

The lifecycle concept links:

- Product and Process Development
- Qualification of the commercial manufacturing process
- Maintenance of the process in a state of control during routine commercial production.

➢ **Supports process improvement and innovation through sound science.**

II. Background - Process Validation and Drug Quality

- The basic principle of GMP is that a drug should be produced that is fit for its intended use.

  - Quality, safety, and efficacy are designed or built into the product.
  - Quality cannot be adequately assured merely by in-process and finished-product inspection or testing
  - Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

III. Objectives of the Cleaning Process

Why Do We Clean?

- Maintain batch identity (control carry-over)
- Control cross-contaminations (Multi-purpose facility)
- Control bio-burden & endotoxin
- Remove API decomposition residues.
- Remove cleaning agents and any other processing aids that can adulterate the product.
- Expectation of Regulators and GMP.

  - Cleaning Validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing of pharmaceutical products or active pharmaceutical ingredients (APIs).

  - Objective of the Cleaning Validation is the confirmation of a reproducible & reliable cleaning procedure that enables the manufacturer to produce product that meets the Critical Quality Attributes.

III. What are we trying to clean away?

Residue Types in a BioPharma Manufactuing Process.

- Cells (animal or microbial)
- DNA
- Proteins
- Degradents
- Endotoxins
- Bioburden

Other Residue Types in a BioPharma Manufactuing Process.

- Processing Aids
  - Antifoams
  - Lubricants
- Excipients
- Preservatives
- Cleaning Solution Residues

III. How clean does it have to be? Acceptance Criteria.

Acceptance Criteria - The three most commonly used criteria are :

- **Visually clean. No residue visible on equipment after cleaning.**
- **No more than 10 ppm of one product will appear in another product .**
- **No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product. - Supplementary Training Modules on Good Manufacturing Practice, Cleaning Validation, World Health Organization, Feb 2009, Kampala, Uganda**

Risk Based Acceptance Criteria (Mollah & White)

- Maximum allowable carryover (MACO) and safety factors
- Process risk versus patient risk
- Manufacturing stage (pre, post, and during purification)
- Cross-contamination between products or product intermediates
- Single vial concept and worst-case cleaning

III. How clean does it have to be? Acceptance Criteria.

Risk Based Acceptance Criteria Thoughts

- Visually Clean is an important criterion. It is possible to have equipment that tests as “Clean” but is visually soiled. Microbal Fermentors are notorious for this condition.

- Patient Risk is an important consideration. Some products (vaccines, hormones, EPO, Diabetes treatments are very potent at low mass doses. Antibiotics have a low threashold for allergenic reactions. Product specific acceptance criteria should consider this. Toxicilogy based limits or limits based on No Observable Effect Limit (NOEL) should be considered.

III. Acceptance Criteria (2)

Maximum Allowable Carry-Over (MACO) Sample calculation:

Single Dose of product A = 7 mg/mL

Batch size of subsequent product B = 100 L

Approach by: JR Voss, Cleaning Validation Acceptance Criterion - Case Study, Boston Area Chapter ISPE, Feb 1999

MACO = 7 mg/mL x 0.1% = 7 ug/mL of A

100L of B x 7 ug/mL = 700 mg allowable carry over of A to a batch of B

What is the rinse limit after we CIP for A prior to making a batch of B?

Final Post A CIP rinse = 10 L

700 mg / 10L = 70 mg/L (70 ppm) of A in the post CIP rinse sample

- **10.1 The fabricator's rationale for selecting limits for product residues should be logical and based on the materials involved and their therapeutic dose. The limits should be practical, achievable, and verifiable.- Guidance Document, Cleaning Validation Guidelines, GUIDE-0028, January, 1 2008, Health Canada, Health Products and Food Branch Inspectorate**

IV. Validation Master Plan

- **4.3.1 A Validation Master Plan is a document that summarizes the firm's overall philosophy, intentions and approach to be used for establishing performance adequacy,** PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S), RECOMMENDATIONS ON VALIDATION MASTER PLAN INSTALLATION AND OPERATIONAL QUALIFICATION NON-STERILE PROCESS VALIDATION, CLEANING VALIDATION PI 006-3, 25 Sept. 2007

- **The requirements for a Cleaning Validation Program should be defined and documented in a master plan or equivalent document.** - Points to Consider for Biotechnology Cleaning Validation,Technical Report No. 49, 2010 Parenteral Drug Association

- The key elements of a qualification and validation program of a company should be clearly defined and documented in a Validation Master Plan.
- The Cleaning Validation is an extension of the VMP.

V. Cleaning Validation – Life Cycle Approach

- Stage 1 Process Design
  - Building and Capturing Process Knowledge & Understanding
  - Prospective Validations
  - Facility Design
  - Methods Development
- Stage 2 Cleaning Process Qualification
  - Cleaning Process Performance Qualification (PPQ)
    - Cleaning Performance Qualification Protocol
    - Process Performance Protocol Execution & Report
- Stage 3 Continued Process Verification
  - Ongoing Monitoring
  - Cleaning assessment due to process or equipment change
  - Cleaning assessment due to gaps.

V. Cleaning Validation Stage 1 CV Design

- Prospective Validations (Lab Scale Studies)
  - Conducted before a new product is released for distribution or, before a product made under a revised manufacturing process is released for distribution.
  - Development of scaledown models / model soils.
  - Materials of construction (MOC) compatibility with product and cleaning solutions
  - Cleaning Agent Selection
  - Cleaning Methodology
    - CIP or COP? Manual or Automated?
  - Product Contact Surfaces
    - Indirect contact surfaces – Buffers & Media

- Swab & Rinse Sample Recovery
  - Swabbing and Rinse Recovery analysis is used to determine the level cleanliness.
  - A recovery study is performed to demonstrate that the residue can be recovered by these methods.
  - WHO guidelines 80% Good, 50% reasonable, <50% is Questionable

V. Stage 1 – Some Equipment Considerations

- Eqiupment Design
  - Sanitary Design
    - Designed to be cleaned – no crevasses deadlegs or shadowing
    - Smooth product contact surfaces - minimizes adsorptive area.
  - Design for drainability (sloped piping), Low point Drains
- Materials of Construction
  - Process Fluid Interactions - Should not be:
    - Reactive
    - Absorptive
    - Additive
  - Seals, Gaskets, hoses, valves, etc. should not add contamination.
  - Cleaning Agents compatible with MOC

V. Stage 1 Cleaning Agents and Process

- Typical Cleaning Agents
  - Alkaline Chemical (NaOH)
  - Acidic Chemical (Phosphoric acid)
  - Oxidizer Chemical (NaOCl, >pH 7)
  - Detergent Formulation (CIP100, CIP200, Tergazyme etc)
  - Water

- Cleaning Agent Activity
  - Proteolyic attack, solubilization of lipid
  - Hydrolysis of protein and solubilization of DNA.
  - Oxidation and proteolysis
  - Solubilization and emulsification
  - Solubilization

- Cleaning Agents – Selection Criteria
  - Suitability to remove product residues
  - Compatibility with the equipment MOC
  - Ease of removal and verification of removal
  - Low toxicity

V. Stage 1 CV Design

- **If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenario.,**
  Validation of Cleaning Processes (7/93) GUIDE TO INSPECTIONS VALIDATION OF CLEANING PROCESSES, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm

- Grouping Strategy
  - Validations of individual unit operations x multiple products – Time & Effort Intensive.
  - Grouping Strategy (Matrixing, Bracketing) is a risk based approach to CV.
  - Reduces the validation workload, while maintaining assurance that the acceptance criteria are met.

- **Cleaning procedures for products and processes which are very similar do not need to be individually validated…It is considered acceptable to select a representative range of similar products and processes. .- Guidance Document, Cleaning Validation Guidelines, GUIDE-0028, January, 1 2008, Health Canada, Health Products and Food Branch Inspectorate**

V. Stage 1 CV Design

- Equipment Grouping Strategy Example
  - From: Risk-Based Cleaning Validation in Biopharmaceutical API Manufacturing, A. Hamid Mollah, Ph.D., Edward K. White, BioPharm International, Nov. 1, 2005,

Group ID	System Description
Media Preparation Tanks	Tanks used for media preparation
Media Hold Tanks	Tanks used for media holds
Bioreactors	Bioreactor used for API manufacturing
Bioreactor Lines	Lines used for bioreactor feed and harvest transfer
Purification Buffer Preparation Tanks	Tanks used for buffer preparations
Purification Buffer Hold Tanks	Tanks used for buffer preparations
Purification Skids	Skids used for purification process

- Product Grouping Strategy
  - Products may also be grouped in terms of “Worst Case” to clean.
- Use Risk Based tools for Justification
  - Failure Mode & Effects Analysis (FMEA), Fault Tree Analysis

V. Stage 1 CV Design

- Considerations for Purification Skids (TFF & Chromatography)
  - Media (resin/membranes) is re-used over many batches due to economic concerns.
  - Media is cleaned between runs or after a fixed number of “cycles” in order to maintain separation / purification efficiency.
  - Media is most often “cleaned in place”.
  - Rely on vendor recommendation for cleaning reagents and conditions.
  - Integration of equipment into central CIP system must be done carefully to avoid sub-optimal unit operation perfomance.
  - Non-sterile operations (UF & Chrome) – Cleaning and Sanitization – objective is bioburden control.

Sample Cleaning Protocol - New Membrane Preparation for Cassettes

Use a feed rate of 323 L/m2/hr (0.5 L/min/ft2)
Control retentate pressure to a fixed setpoint that gives approximately 30% conversion

Volume	Mode	Solution	Time
2 L/ft2	Single Pass Flush	Pure Water	N/A
1 L/ft2	Single Pass Flush	Cleaning Solution	N/A
0.5 L/ft2	Total Recycle, then flush & drain	Cleaning Solution	30 minutes
1 L/ft2	Single Pass Flush	Pure Water	N/A
0.5 L/ft2	Total Recycle, then flush & drain	Sanitizing Solution	30 minutes
1 L/ft2	Single Pass Flush	Pure Water	N/A
0.5 L/ft2	Total Recycle and NWP	Storage Solution	15 minutes

*If an Integrity Test is needed, it is performed after the water flush before storage solution recycle

Sample Cleaning Protocol – Post-Use Cleanout for Cassettes

Use a feed rate of 323 L/m2/hr (0.5 L/min/ft2)
Control retentate pressure to a fixed setpoint that gives approximately 30% conversion

Volume	Mode	Solution	Time
1 L/ft2	Single Pass Flush	Cleaning Solution	N/A
0.5 L/ft2	Total Recycle, then flush & drain	Cleaning Solution	30 minutes
1 L/ft2	Single Pass Flush	Pure Water	N/A
0.5 L/ft2	Total Recycle, then flush & drain	Sanitizing Solution	30 minutes
1 L/ft2	Single Pass Flush	Pure Water	N/A
0.5 L/ft2	Total Recycle and NWP	Storage Solution	15 minutes

*If an Integrity Test is needed, it is performed after the water flush before storage solution recycle

V. Stage 1 Cleaning Process Design & Procedures

- Cleaning Process Modes:
  - Clean-In-Place (CIP)
  - Clean-Out of Place (COP)
  - Automated
    - CIP – CIP Skid with Integrated Feed/Return Piping Circuits
    - COP – Parts Washer with Automated Cycle
  - Manual
    - CIP – portable CIP Skid
    - Manual Disassembly & Washing by Operator.
- Procedures - Cleaning Cycle should have written controlled procedures
  - Cleaning Cycle is defined by :
    - Contact Time
    - Temperature
    - Cleaning Reagent Concentration
    - Action (Flowrate, Pressure, Turbulence, Manual Scrubbing)

V. Stage 1 Cleaning Process Procedures

- Cleaning Procedures:
  - Avoid COP with Manual Washing by Operators
  - Highest Source of Variability
  - Need Specific Procedures (How to scrub, which utensil to use, when to replace utensil, High Scrutiny, Training & Re-Training.
- Reagent Control
  - Expiration Dates

V. Stage 1 - Cleaning Process Variability & Controls

- Sources of Variation in Cleaning Validation
  - Cleaning agent quality
  - Concentration of cleaning agent
  - Water/solvent quality
  - Time(s)
  - Temperature
  - Pressure (spray device)
  - Flow
  - Rinse conditions
  - Dirty hold time
  - Clean hold time
  - Campaign length
  - Manufacturing conditions
  - Operator for manual cleaning

From; Webinar- How Will the FDA Process Validation Guidance Affect Cleaning Validation, Destin A. LeBlanc Cleaning Validation Technologies, May 2012

- Control of Variation in Cleaning Validation
  - Select Cleaning Process Parameters(CPP) that minimize variation – Overkill. (Design space Studies)
  - Many of these can be established by adequate lab cleaning studies (multiple lots of cleaning agent, stress at lower concentrations, temperatures, & times, dirty hold conditions)
  - Others established by computer simulations (spray device suitability) or engineering principles (flow rate)
  - Document evaluation!

V. Stage 1 Cleaning Process Design

Critical Process Parameters	Critical Quality Attributes
• Process temperature	• Visual detection or limits
• Process pressure	• Cleaning agent residues
• Process flow	• Product residues
• Process time	• Microbiological residue limits
• Cleaning agent concentration	• Drainability/drying
• Dirty hold time (soil condition)	• Conductivity/resistivity
• Clean hold conditions	

- Cleaning Processes – A series of steps:
  - Commence Cleaning Process before “Dirty” Hold Time Expires
  - Water rinse to remove loose soils.
  - Cleaning solution(s) wash (perhaps with rinses in between)
  - Final Water Rinse (sampling step)
  - Drain and or Dry
  - Hold in a state of cleanliness until used or Clean Hold Time expires

V. Stage 1 Analytical Methodolgy

…analytical methods should be:

- **Specific**
- **Sensitive**
- **Accurate**
- **Provide results that are reliable.**
- **Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described**.- **Guidance for Industry Process Validation: General Principles and Practices, January. 2001, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Current Good Manufacturing Practices (CGMP) Revision 1**

- Most common Process Analytical Techniques (PAT)
  - Conductivity
  - pH
  - Total Organic Carbon
  - Others (Chlorine Assay Kit, Detergent Surfactant Kit, protein assay kit)
  - HPLC, FTIR, ELISA , total protein & Endotoxin
  - Are Specific Assays the Most Appropriate?

V. Stage 1 Sampling Methodolgy

- Most common Sampling Schemes
  - Rinse Samples (indirect)
  - Swabbing (direct)
  - Can be a combination of both.
- Sampling Systems
  - Sampling technology should not contaminate or cause contamination of sample
  - Examples; Novaseptum, Sta-Pure etc. for Rinse samples

Sampling Method	Pro's	Con's
Rinse	Maintains System Closure	Relies on uniform distribution of residue and covereage of reinse step
	Rinse represents all contact areas eve the "hard to reach"	Does not directly sample surface
	Analysis can be on-line or off-line	
Swab	Direct Sample of Surface	Risk of contamination higher with direct operator interface
	Sampling spot is defined	Analysis off line
		Must have very well defined procedures, training

V. Stage 2. Cleaning Process Qualification

- When?
  - Usually run concurrently with Process Performance Qualification (Process Validation).
  - After Installation Qualification & Operational Qualification.
- What?
  - There should be a written Cleaning Validation Protocol to guide and document the CV. The following sections have been suggested for the protocol:
    - Background
    - Purpose
    - Scope
    - Responsibility
    - Sampling procedure
    - Testing procedure
    - Acceptance criteria
    - Deviations

From; Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants, Dec. 2000, Active Pharmaceutical Ingredients Committee, CEFIC

V. Stage 2. CV Protocol

- Background
  - Equipment & Product Grouping Strategy & Justification of “Worst Case”
  - Equipment Description
  - Cleaning methods for each system or unit operation
  - Cleaning Agents
- Purpose/Objective
  - Validation Objective
- Scope
  - Testing Descriptions for Each System or Unit Operation
    - Dirty Equipment Hold Time (DEHT) – Time btwn end of production to beginning of Cleaning Procedure
    - Clean Equipment Hold Time (CEHT) – Time interval beyond which the cleaned equipment must be re-cleaned
  - Justification of the number of consecutive cleaning runs that demonstrate Cleaning Process Validation.
  - Exclusions / Exceptions
  - Cleaning Validation Report Outline

V. Stage 2. CV Protocol

- Responsibility
  - Schedule Validation Activities
  - Cleaning Performance
  - Sample Acquisition
  - Sample Analysis
  - Review of Data, Protocol & Report Approval

- Sampling Procedures
  - Swab sampling SOP for each System / Unit Operation & Sampling Locations
  - Rinse Sampling SOP for Each System & Unit Operation
  - Volume of Rinse for Each System & Unit Operation
  - Rinse Sample Volume
  - Sample ID/Documentation

V. Stage 2. CV Protocol

- Testing Procedures
  - Test Methods and Procedures for both Swab Samples & Rinse Samples
    - Product & Cleaning Agent Residues
  - Note the limits of detection and quantitation for the tests being performed.
  - Recovery Correction Factor Calculation (If recovery study indicates sampling method recovers less that 100%)
  - Samples below the Limit of Quantitation (LOQ) but above the Limit of Detection (LOD) use LOQ value in residue calculations.
  - Samples below the Limit of Detection (LOD) use LOD value in residue calculations.
  - Review of Data, Protocol & Report Approval.

V. Stage 2. CV Protocol

- Acceptance Criteria
  - Document Acceptance criteria, including the rationale for setting the specific limits
  - Equipment must be visually clean.
- Deviations
  - Document Planned or Unplanned Deviations from Protocol.
  - Plan for what to do in case of failure of part of the protocol.

V. Stage 3 Continued Process Verification

- Process Verification Tools
  - Cleaning assessment due to process or equipment change.
  - Risk based sampling and monitoring
  - Data Tending Review
  - Cleaning assessment due to gaps.
  - Training

- Cleaning assessment due to process or equipment change.
  - Changes to the process, product or equipment should trigger a Cleaning Assessment Review. Do the proposed changes to the process or equipment impact the Cleaning Validation?
  - Additional Work to close gap or Re-validate?

V. Stage 3 Continued Process Verification

- Risk-Based Sampling and Monitoring
  - Validation runs will have enhanced monitoring
  - Once the process is validated a reduced sampling & testing may be implemented.
  - Reduced sampling plan should be justified with Risk Assessment.
- Data Trending Review
  - Cleaning data should be trended and assessed.
  - Trending techniques such as Process Capability / Statistical Process Control can be used to identify potential issues before an Alarm or Out of Specification event occurs.
  - Investigation Procedure for adverse trends.

V. Stage 3 Continued Process Verification

- Cleaning assessment due to gaps.
  - Periodic assessment of the Cleaning Validation against updated requirements.
  - Additional Work to close gap or Re-validate?

- Training
  - Operators should be trained and qualified in sampling techniques.
  - Operators involved in manual cleaning operations should be trained.
  - Periodic re-qualification should be considered.

VI. Cleaning Validation Summary

- Cleaning Validation promotes product and patient safety.
- The Cleaning Validation demonstrates that the cleaning process adequately and consistently removes product, process and environmental residues from the cleaned systems so they can be used for the manufacture of subsequent products.
- Cleaning Validation can be aligned to a validation lifecycle approach that encompasses development, qualification and validation phases.
- Cleaning Validates supports process improvement and innovation through sound science.
- A Grouping Strategy (Matrixing, Bracketing) is a risk based approach to CV that reduces the validation workload, while maintaining assurance that the acceptance criteria are met.

Selected References

Supplementary Training Modules on Good Manufacturing Practice, Cleaning Validation, World Health Organization, Feb 2009, Kampala, Uganda

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